Regulatory Considerations for Post-Approval Manufacturing Changes and the Utility of Change Protocols – FDA Perspective

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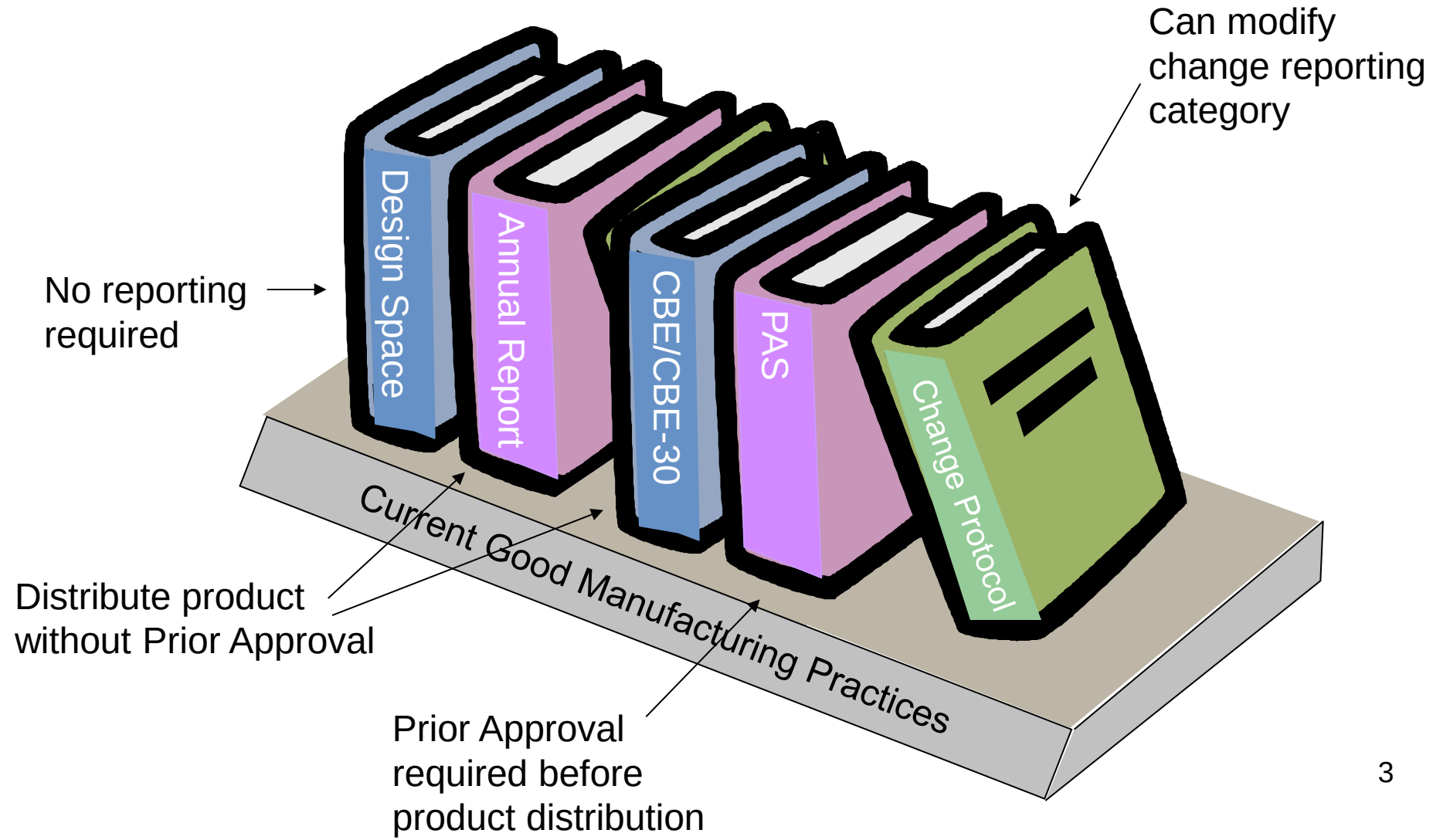
Outline

- Background on FDA change management regulation and guidance
- Change protocols - requirements and opportunities
- Potential future directions

FDA Pathways to Pharmaceutical Manufacturing Changes



Change Regulations

The applicant must notify FDA about each change in each condition established in an approved application beyond the variations already provided for in the application…

- **Prior Approval Supplements (PAS)** – 21 CFR 314.70 (b)
  A supplement must be submitted for any change in the drug substance, drug product, production process, quality controls, equipment, or facilities that has a **substantial potential** to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product.
- **Changes Being Effected (CBE/CBE-30)** – 21 CFR 314.70 (c)
  A supplement must be submitted for any change …. that has a **moderate potential** to have an adverse effect on the identity, strength, quality, purity, or potency...
- **Annual Report (AR)** - 21 CFR 314.70 (d)
  Changes … that have a **minimal potential** to have an adverse effect on the identity, strength, quality, purity, or potency … must be documented by the applicant in the next annual report…

Guidances Related to Change Management

- Changes to an Approved NDA or ANDA (2004)
  - Gives example listing of many changes and related reporting categories
  - Companion Guidance Documents:
    - Changes to an Approved NDA or ANDA: Questions and Answers (2001)
    - Changes to an Approved NDA or ANDA; Specifications – Use of Enforcement Discretion for Compendial Changes (2004)
    - CMC Postapproval Manufacturing Changes Reportable in Annual Reports (DRAFT, 6/24/2010)
- SUPAC Guidances
  - Provide both change categories and method of evaluation of the effects of the change
  - Specific to dosage form type
- Draft Comparability Protocol Guidance
  - Comparability Protocols – Chemistry, Manufacturing and Controls Information (DRAFT 2/25/03)

Guidances Related to Change Management - SUPAC

- **SUPAC-IR:** Immediate Release Solid Oral Dosage Forms: Scale Up and Post-Approval Changes: Chemistry, Manufacturing and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation (1995)
  - SUPAC-IR Questions and Answers about SUPAC-IR Guidance (1997)
- **SUPAC-MR:** Modified Release Solid Oral Dosage Forms: Scale Up and Post-Approval Changes: Chemistry, Manufacturing and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation (1997)
  - SUPAC-IR/MR: Immediate Release and Modified Release Solid Oral Dosage Forms Manufacturing Equipment Addendum (Draft, 1999)
- **SUPAC-SS:** Nonsterile Semisolid Dosage Forms: Scale Up and Post-Approval Changes: Chemistry, Manufacturing and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation (1997)
  - SUPAC-SS: Nonsterile Semisolid Dosage Forms Manufacturing Equipment Addendum (Draft, 1998)
- **PAC-ATLS:** Postapproval Changes – Analytical Testing Laboratory Sites (1998)

Status of Current FDA Regulatory Approaches

- Most FDA change guidances are now 1-2 decades old
  - Assumes that all products within a drug product category have same risk
  - Often overly conservative; occasionally overly liberal
  - No leeway for well understood risks to product quality or process
- Science and risk based approaches under QbD have evolved pharmaceutical manufacturing
  - Currently, no additional flexibility beyond approved design space for post-approval changes

Protocol Regulations – NDAs & ANDAs

Change Protocols for NDA/ANDA- 21 CFR 314.70 (e)

- An applicant may submit one or more protocols describing:
  - specific tests
  - studies
  - acceptance criteria

  to demonstrate the lack of adverse effect on the identity, strength, quality, purity, and potency of the drug product
- Can be included in an NDA or as a PAS
- Justifies a reduced reporting category for the change
  - Reduces the potential risk of an adverse effect
  - Does not waive reporting of change

Protocol Regulations – BLAs

Change Protocols for BLAs – 21 CFR 601.12(e)

- An applicant may submit one of more protocol describing:
  - specific tests
  - validation studies
  - acceptance limits to be achieved

  to demonstrate the lack of adverse effect for specified types of manufacturing changes on the identity, strength, quality, purity or potency of the product
- Protocols and changes to protocols to be submitted as a PAS
  - Also accepted in original BLAs
- Justifies a reduced reporting category for the change
  - Reduces the potential risk of an adverse effect
  - Does not waive reporting of change

Why use a Change Protocol?

- Allows for reduced reporting categories of post-approval changes
- Enables faster distribution of product after a manufacturing change
  - Eases coordination with multiple health authorities
- Achieve early agreement on change plan from regulators
- Allows multiple changes or repetitive implementations of a specific change

How to File a Change Protocol

- Recommend inclusion in regional section of application (3.2.R)
- Mention in cover letter for a supplemental application
- Recommend mentioning in the Quality Overall Summary and main text of the application for an original application
  - Aids the reviewer in timely identification and review of the protocol
- Changes to an approved change protocol must be made as a Prior Approval Supplement

When are protocols appropriate?

- When an applicant wishes to make future changes beyond the alternatives/variations approved in the application
- When the applicant understands the potential risks of the change and how to evaluate them
  - How will effects of change be evaluated?
  - What determines the success of a change?
- For changes that will not require efficacy, safety or pharmacokinetic evaluation

Potential of Change Protocols

- Change protocols have the potential to enhance regulatory flexibility and ease post approval changes
- Opportunity to facilitate continual improvement and process optimization
- Synergy with understanding obtained in Quality by Design (QbD) approaches

Risk Based Approach

- Understand relationships and risks between:

  Patient ⟺ Product ⟺ Manufacturing Process

- Risk assessments can be supported by laboratory or pilot scale data
- Potential to use change protocols to support a wide breadth of changes:
  - Optimize process
  - Support continual improvement
  - Provide flexibility in scale/throughput

Simplified Examples of Risk Assessment for Change Management

Film-coated IR tablet made by blending/direct compression

CASE 1: Low dose drug (0.5% drug loading)
Highly stable API

Drug Product CQA	Blending	Compression	Coating
Description	N/A	Low	Low
Identification	N/A	N/A	N/A
Assay	N/A	N/A	N/A
Content Uniformity	High	Moderate	N/A
Degradation	N/A	N/A	Low
Dissolution	N/A	Moderate	Low
Microbiology	N/A	N/A	Low

CASE 2: High drug loading (~40%)
Moisture sensitive API

Drug Product CQA	Blending	Compression	Coating
Description	N/A	Low	Low
Identification	N/A	N/A	N/A
Assay	N/A	N/A	N/A
Content Uniformity	Low	Low	N/A
Degradation	N/A	N/A	High
Dissolution	N/A	Moderate	Low
Microbiology	N/A	N/A	Low

Examples of Protocol Approaches for Risk- Based Manufacturing Changes

- For each unit operation, or group of operations, describe:
  - Types of changes that could be performed under the protocol (e.g., parameters ranges, scale, equipment type)
  - Potential risk of change
  - Studies to be performed
  - Acceptance criteria for the change
- Alternatively, for each CQA, describe:
  - The types of changes that might affect that attribute
  - Potential risk of change
  - Studies to be performed
  - Acceptance criteria for the change
- Other example changes:
  - Raw material attributes/specifications

Considerations for Protocols

- Potential risk of the change on the critical quality attributes of the product
  - Evaluate effects downstream of change
- Possibly grouped together based on:
  - Unit operation
  - Potential effect to product CQAs
- Ability of control strategy to detect the effect of the change
  - Is enhanced sampling or non-routine tests needed to verify product quality?
- Suitability of the change throughout all regions of potential operations (e.g., design space)

Potential of Harmonization of Post-Approval Changes

- Both EMA and FDA have regulations for protocols that can reduce reporting categories
- EMA and FDA have an ongoing pilot for “Parallel Assessment” or “Consultative Advice” for QbD containing applications
  http://www.fda.gov/downloads/InternationalPrograms/FDABeyondOurBorders ForeignOffices/EuropeanUnion/UCM259808.pdf
- FDA and EMA are considering extending the pilot beyond March 2014
  - Focus on protocols for flexibility of post-approval changes

Conclusions

- Protocols provide a flexible pathway to reduce reporting categories for changes to an approved application
- Risk based approaches facilitates the level of understanding needed to submit broader change protocols
- ONDQA is accepting change protocols in original and supplemental NDAs
  - Potential to include in the ongoing EMA-FDA pilot
  - **Discussion prior to submission is highly recommended**

Thank you!

Questions, comments, concerns:

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